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13. SUPPLEMENTARY NOTES

Distinguishing whether traditional ovarian cancer risk factors differ by tissue of origin (ovarian vs. fallopian) may further our understanding of these pathways. Likely tissue of origin can be estimated from pathology reports by presence or absence of a two-fold difference in tumor size between ovaries. We applied this classification algorithm to ovarian cancer cases in a population based case-control study (NEC) and two prospective cohort studies (NHS/NHSII). We used polytomous logistic regression (for NEC) and competing risks models (for NHS) to estimate associations. Among the 1801 invasive epithelial cases, we observed 1127 tumors with a dominant mass, indicating a greater likelihood of ovarian origin, and 674 with no dominant mass, indicating a greater likelihood of fallopian tube origin. The dominant cases were more likely to be mucinous, endometrioid, clear cell, or undifferentiated while the non-dominant cases were more likely to be serous invasive ovarian cancers. Our results suggest that tubal ligation and parity may be more strongly associated with tumors of ovarian origin, while family history of ovarian cancer and possibly past smoking primarily increases risk of tumors of tubal origin. Furthermore, our data suggest aspirin and NSAID use may be more strongly associated with tubal tumors.

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ovarian cancer, risk factors, fallopian tube, origin

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Introduction

Ovarian cancer is a deadly and heterogeneous disease. Identifying epidemiologic and genetic characteristics related to disease risk may lead to screening or treatment strategies that could save lives. Although some epidemiologic associations are established, like risk reduction with parity and oral contraceptive use, the influence of other characteristics like body mass index and common genetic variants is less clear. Distinguishing categories of ovarian cancer based on shared pathways of development may clarify these associations and further our understanding of the disease. Recent research has suggested that some ovarian cancers may develop from the fallopian tubes while others develop from the ovarian surface epithelium through Mullerian inclusions or endometriosis implants. In this study, we will evaluate the influence of reproductive and lifestyle characteristics on cancers that develop from the fallopian tubes versus the ovarian surface epithelium using tumor dominance ascertained from pathology reports as a surrogate. Next we will examine genetic susceptibility and survival by these same cell of origin categories. In tandem, we will evaluate each of these associations (epidemiologic predictors, genetic susceptibility, and survival) by histologic subtype categorized into the following molecular pathways: 1) Mullerian inclusions that undergo K-RAS and BRAF mutations leading to low grade serous and mucinous carcinomas, 2) endometriosis implants or transformation into endometrioid epithelium leading to serous, clear cell, or endometrioid carcinoma, 3) fallopian tube that undergoes DNA damage as a result of ovulations or other recurrent stress leading to p53 mutations, serous intraepithelial carcinoma and ultimately metastatic serous carcinoma. Through these analyses, we hope to clarify the predictors and pathways of ovarian cancer.

Body

In accordance with my proposed Statement of Work, my research aims will be accomplished through three main tasks and associated subtasks. In the first task, I will evaluate the influence of reproductive and lifestyle characteristics on categories of ovarian cancer. We have made significant progress on this task including the completion of pathology report abstraction to identify tumor dominance in cases (task 1a), we have performed statistical analyses in SAS (task 1b), I have reviewed results of these analyses with mentors (task 1d) and am in the process of preparing a manuscript of these results (task 1c). Although not included in my original proposal, we were able to partner with collaborators from the Nurses' Health Study who were doing similar work funded through other sources, allowing us to increase our sample size and validate our findings in an independent and prospectively collected study population.

Briefly, we evaluated the relation between epidemiologic variables and tumor dominance in two study populations (for details see poster and PowerPoint presentation in appendices A and B). The New England Case Control (NECC) study is a population based case control study with over 2000 cases and 2000 controls age 18 and older from eastern Massachusetts and New Hampshire between 1992 and 2008. Cases were incident cases of ovarian cancer identified through hospital tumor boards and cancer registries. Controls were identified through a combination of random digit dialing, townbooks (population registries) in Massachusetts, and driver's license lists in New Hampshire. Participants were interviewed in person on a wide range of reproductive and lifestyle factors at enrollment. The Nurses' Health Study and Nurses' Health Study II are cohort studies of nurses throughout the United States followed biennially with mailed questionnaires on a wide range of exposures. The original Nurses' Health Study started in 1976 with 121,000 women aged 30-55 and the Nurses' Health Study II started in 1989 with 116,000 women aged 25-42. All study participants are followed for various outcomes including ovarian cancer. In the combined Nurses' Health Study cohorts (NHS) there were 885 incident cases of ovarian cancer.

Tumor dominance was determined based on pathology reports using the following classification criteria. Cases in which the tumor was limited to one ovary or when one ovary exceeded the other in dimension by more than

two times were considered dominant tumors (DOM+) and likely of ovarian origin. Cases that did not meet this criteria or with disease equally distributed across the peritoneal cavity were considered non-dominant tumors (DOM-) and likely of tubal origin. We were able to abstract dominance data from 1164 cases (1312 invasive, 352 borderline) from NECC and 509 cases (392 invasive, 117 borderline) from the NHS. Analyses were restricted to invasive cases. We used polytomous logistic regression (NECC) and competing risk analyses (NHS) to evaluate the association between exposure and dominant or non-dominant ovarian cancer adjusted for age, oral contraceptive use, parity, tubal ligation, and family history of breast or ovarian cancer. For each exposure, we compared a model with separate estimates for dominant and non-dominant tumors to a model with a single estimate for all cases and used a likelihood ratio test to determine a p for heterogeneity.

Among invasive cases we observed 1048 dominant cases (778 NECC, 270 NHS) and 656 non-dominant (534 NECC, 122 NHS). Dominant tumors were more likely to be borderline tumors, mucinous, endometrioid, or clear cell while non-dominant tumors were more likely to be low-grade or high-grade serous tumors. Oral contraceptive use was associated with a decreased risk of both dominant and non-dominant tumors with the strongest reduction in risk for women who used oral contraceptives for five years or longer (Table 1). The birth of one child was equally protective for dominant and non-dominant tumors but for subsequent pregnancies the association was stronger for dominant tumors. The birth of four or more children was associated with a 72% reduction in risk of dominant tumors but only a 51% reduction in risk of non-dominant tumors (p for heterogeneity = 0.004). For several reproductive factors, including tubal ligation (p for heterogeneity = 0.0002), hysterectomy (p for heterogeneity = 0.18), and endometriosis (p for heterogeneity = 0.0002), we observed significant associations only with dominant tumors. Interestingly, IUD use was associated with a non-significant decreased risk of dominant tumors (OR=0.83, 95% CI: 0.65 - 1.05) and a non-significant increased risk of non-dominant tumors (OR= 1.71, 95% CI: 0.64 - 4.57). The association between IUD use and non-dominant tumors was stronger in the NHS cohorts (OR=3.08, 95% CI: 1.35 – 7.05) and not significant in the NECC population (OR=1.11, 95% CI: 0.86 – 1.45), though heterogeneity between tumor types was observed in both study populations (NHS p for heterogeneity = 0.06, NECC p for heterogeneity = 0.05).

Table 1. Association between reproductive characteristics and ovarian cancer, by tumor dominance as surrogate for cell of origin, New England Case Control Study (1992-2008), Nurses' Health Study (1976-2006), and Nurses' Health Study II (1989-2007)

Variable	DOM+ RR (95%CI)	DOM- RR (95%CI)	$p_{heterogeneity}$
OC use			
Never	Ref	Ref	
< 5 years	0.86 (0.65, 1.13)	0.93 (0.76, 1.13)	0.22
≥ 5 years	0.65 (0.35, 1.22)	0.55 (0.37, 0.73)	0.71
IUD use	0.83 (0.65, 1.05)	1.71 (0.64, 4.57)	0.02
Tubal ligation	0.60 (0.49, 0.75)	1.02 (0.81, 1.28)	0.0002
Hysterectomy	0.67 (0.53, 0.86)	0.87 (0.65, 1.15)	0.18
Parity			
None	Ref	Ref	
One	0.60 (0.47, 0.76)	0.62 (0.45,0.85)	0.91
Two	0.48 (0.36, 0.65)	0.67 (0.52, 0.85)	0.004
Three	0.32 (0.26, 0.41)	0.57 (0.43, 0.75)	0.0003
≥ Four	0.28 (0.19, 0.39)	0.49 (0.26, 0.92)	0.004
Endometriosis*	1.49 (1.12, 1.97)	0.68 (0.45, 1.02)	0.0002

*assessed in NECC only

Table 2. Association between IUD type and duration and ovarian cancer risk by tumor dominance as a surrogate for cell of origin, New England Case Control Study (1992-2008).

IUD type	Controls n=2101	DOM+ n=778		DOM- n=534		$p_{heterogeneity}$
Non-iud user	1295 (82)	526 (86)	1.00	327 (83)	1.00	
plastic	70 (6)	18 (3)	0.72 (0.42, 1.24)	18 (5)	1.17 (0.68, 2.01)	
copper	90 (6)	37 (6)	1.08 (0.72, 1.63)	20 (5)	0.94 (0.57, 1.57)	0.2
unknown	122 (8)	33 (5)	0.77 (0.51. 1.16)	31 (8)	1.17 (0.76, 1.78)	
progesterone	1 (<1)	1 (<1)	**	0	**	
IUD duration*						
Non-IUD user	1747 (83)	678 (87)	1.00	445 (83)	1.00	
<1 year	106 (5)	35 (5)	0.99 (0.66, 1.48)	26 (5)	1.12 (0.72, 1.76)	
1-3 years	96 (5)	19 (2)	0.60 (0.36, 1.00)	24 (4)	1.17 (0.72, 1.85)	
4-6 years	63 (3)	12 (2)	0.57 (0.30, 1.08)	15 (3)	1.09 (0.61, 1.95)	
>6 years	88 (4)	33 (4)	1.00 (0.66, 1.52)	24 (4)	1.11 (0.69, 1.78)	0.13

*Restricted to phases 2 and 3 of NECC (1578 controls, 615 dominant cases, 396 non-dominant cases)
Note: there are 2 iud users (both from ovca4) with missing duration

Data on type of IUD used was only available in the NECC study. The association did not appear to vary by type of IUD used (Table 2). As shown in table 3, nurses who used IUDs for a short duration had no increase risk of either type of tumor while women who used IUDs for a longer time (approximately 8 or more years) had no increased risk of dominant tumors but a four-fold increased risk of non-dominant tumors (OR=4.18, 95% CI: 1.83 – 9.57). This difference was not evident in NECC (table 2). Differences between the studies may be attributable to prospective design of the NHS cohorts that allow inclusion of even the most aggressive cases.

Table 3. Association between IUD duration and ovarian cancer risk by tumor dominance as a surrogate for cell of origin, Nurses' Health Study (1976-2006), and Nurses' Health Study II (1989-2007)

IUD duration	Dom+	DOM-	$p_{heterogeneity}$
Never	1.00	1.00	0.02
Short	1.12 (0.59, 2.13)	0.77 (0.24, 2.42)	
Long	0.92 (0.30, 2.90)	4.18 (1.83, 9.57)	

The difference in risk by tumor dominance were not as striking for non-reproductive characteristics. Compared to women with a BMI < 23 kg/m^2, women with a BMI between 25 and 29 kg/m^2 were at a reduced risk of non-dominant tumors but no risk of dominant tumors (p for heterogeneity = 0.05). However, we observed no trend

in the association for either tumor type (Table 2). We observed an elevated risk of ovarian cancer regardless of tumor type for current smokers but the association for past smokers was restricted to non-dominant tumors (p for heterogeneity = 0.02). Interestingly, aspirin (p for heterogeneity = 0.07), acetaminophen (p for heterogeneity = 0.04), and other NSAIDs (p for heterogeneity = 0.03) appeared to decrease risk of non-dominant tumors while showing no association or even an increased risk of dominant tumors. As expected, given the literature regarding BRCA mutation carriers and evidence of ovarian cancer developing in the tubes, family history was more strongly associated with an increased risk of non-dominant tumors (OR=2.32, 95% CI: 1.54 – 3.49) than non-dominant tumors (OR=1.40, 95% CI: 0.91-2.16). Associations for all exposures were similar but attenuated when we restricted to serous tumors (data not shown).

Table 4. Association between non-reproductive characteristics with dominant and non-dominant ovarian cancers, New England Case Control Study (1992-2008), Nurses' Health Study (1976-2006), and Nurses' Health Study II (1989-2007)

Variable	DOM+ RR (95%CI)	DOM- RR (95%CI)	$p_{heterogeneity}$
Body mass index (kg/m2)			
<23	Ref	Ref	
23-24	0.98 (0.80, 1.19)	1.07 (0.59, 1.93)	0.72
25-29	0.94 (0.76, 1.16)	0.78 (0.58, 1.04)	0.05
≥30	1.15 (0.94, 1.40)	1.04 (0.76, 1.41)	0.26
Smoking			
Never	Ref	Ref	
Past	0.97 (0.83, 1.13)	1.25 (1.04, 1.51)	0.02
Current	1.30 (1.02, 1.66)	1.37 (1.06, 1.77)	0.95
Aspirin use	0.99 (0.83, 1.18)	0.73 (0.46, 1.15)	0.07
Acetaminophen use	1.24 (1.05, 1.47)	0.90 (0.60, 1.34)	0.04
Other NSAID use	0.88 (0.74, 1.04)	0.66 (0.53, 0.82)	0.03
Family hx of breast cancer	1.23 (1.01, 1.49)	1.19 (0.93, 1.51)	0.96
Family hx of ovarian cancer	1.40 (0.91, 2.16)	2.32 (1.54, 3.49)	0.08

Overall, factors traditionally associated with ovarian cancer risk such as parity, tubal ligation, and endometriosis appear to be most relevant to dominant tumors, those likely of ovarian origin, while family history of ovarian cancer and possibly IUD use are most relevant to non-dominant tumors, those likely of fallopian origin. For non-dominant tumors, the combination of increased risk with IUD use and decreased risk with NSAIDs suggests that inflammation may play a role but this will need to be validated in other studies. I presented the results of this work as a poster (see appendix A) at the Dana Farber Harvard Cancer Center Research Retreat for Breast and Gynecologic cancers and gave a talk on this work in the GYN-ONC Basic Science lecture series in our department in April (see appendix B). We are currently preparing a manuscript of these results. Analyses by histologic categories based on molecular pathways is in development.

The second task in the Statement of Work focuses on the measurement of genetic variation in telomere related genes in relation to ovarian cancer risk. As noted above, we were able to complete data abstraction and assignment of dominant and non-dominant tumor types (task 2a). In addition, we extracted and amplified DNA from cases and controls in the most recent phase of the New England Case Control study (tasks 2b and 2c). Our next step will be to determine the list of SNPs to genotype in task 2d. We are waiting to for results of the GWAS follow-up genotyping, which includes some our samples, to determine which SNPs to genotype for this

proposal. The GWAS follow up results are expected in May 2011 and will be reported at the Ovarian Cancer Association Consortium meeting June 2011. Therefore, we expect to be able to finalize the list of SNPs for our effort shortly thereafter, which will keep us to our originally proposed schedule of genotyping in the second year of this study.

The third task in the Statement of Work focuses on survival. Survival status has been collected on all cases in the New England Case Control study and was last updated in March 2011 for all cases. We are in the process of collecting detailed treatment data on cases diagnosed and/or treated at Brigham and Women's Hospital or Massachusetts General Hospital. To date, we have abstracted data on 557 cases enrolled in the first two phases of the New England Case Control study (1992-2003). Data abstraction on the remaining cases is ongoing.

Key research accomplishments

- Abstraction of tumor dominance data
- Analysis of epidemiologic outcomes by tumor dominance
- Poster presentation and talk on epidemiologic predictors by tumor dominance
- Abstracted detailed survival and treatment data on 557 ovarian cancer cases in our study

Reportable outcomes

- Presentation April 13, 2011 "Epidemiologic predictors of tumor dominance in ovarian cancer, a surrogate for cell of origin" Gyn-Onc Basic Science Lecture Series, Department of Obstetrics and Gynecology, Brigham and Women's Hospital
- Presented two posters at Dana Farber Harvard Cancer Center Research retreat for Gynecologic and Breast cancers
    - **Terry KL**, Kotsopoulos J, Murphy M, Hankinson S, Crum C, Cramer D, Tworoger S. Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. Joint Symposium of the Dana Farber/Harvard Cancer Center Programs in Breast and Gynecologic Cancer, March 25, 2011
    - Harris HR, Cramer DW, Vitonis AF, DePari M, **Terry KL**. Folate, vitamin B6, methionine, and alcohol intake in relation to ovarian cancer risk. Joint Symposium of the Dana Farber/Harvard Cancer Center Programs in Breast and Gynecologic Cancer, March 25, 2011

Conclusions

Our research on "Pathways to understanding ovarian cancer epidemiology, genetic susceptibility, and survival" is proceeding according to schedule. We have met our goals for year 1 including collection and analysis of data regarding epidemiologic predictors of tumor dominance as a surrogate for cell of origin, DNA extraction and amplification, and collection of survival and treatment data. Through this work we have shown that epidemiologic predictors do vary by tumor dominance with reproductive factors traditionally associated with ovarian cancer predicting dominant tumors and family history of ovarian cancer predicting non-dominant tumors. Surprising findings regarding IUD use and NSAIDs suggest an inflammatory pathway for non-dominant tumors (likely of tubal origin) that will need to be validated. We are poised for the next stage of our research which will involve evaluating genetic susceptibility and survival.

Appendix A

Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin

Kathryn Terry[1]*, Joanne Kotsopoulos[2]*, Megan Murphy[2], Susan Hankinson[2], Christopher Crum[3], Daniel Cramer[1], Shelley Tworoger[2]

[1]Obstetrics and Gynecology Epidemiology Center, [2]Channing Laboratory, and [3] Department of Pathology at Brigham and Women's Hospital

*shared first authorship

BACKGROUND

- Ovarian tumors traditionally are thought to arise from the ovarian surface epithelium (OSE); however, recent studies suggest that some tumors may originate in the distal fallopian tube.
- Differences in risk factors for tumors of ovarian versus tubal origin may explain inconsistent associations across studies for some exposures.
- To determine cell of origin in cancer resections, it is necessary to conduct detailed sectioning of fallopian tubes and ovaries, which is impractical in large epidemiologic studies.
- A prior study suggested tumor dominance, determined from pathology reports, may be an acceptable surrogate for cell of origin, such that tumors arising in the OSE are more likely to involve only one ovary or to show one involved ovary exceeding the other in dimension by more than two-fold (DOM+), while tumors of tubal origin show symmetric ovarian involvement or an even distribution across the peritoneal cavity (DOM-)[1].

PURPOSE

- The objective of the current study was to explore whether the associations with known ovarian cancer risk factors vary by tumor dominance, a surrogate for cell of origin (ovarian vs. fallopian).

METHODS

Study Populations:

- Nurses' Health Studies (NHS & NHSII)
  - -Prospective cohort study of female registered nurses with biennial mailed questionnaires to collect data on risk factors on disease events
  - -NHS: 121,700 nurses aged 30-55 followed 1976 to 2006.
  - -NHSII: 116,430 nurses aged 25 to 42 followed 1989 to 2007.
- New England Case Control Study (NECC)
  - -Population based case-control study of ovarian cancer with risk factor data collected by in-person interview
  - -2100 cases and 2029 controls aged 16-79 from New Hampshire and eastern Massachusetts enrolled between 1992 and 2008.

Classification of Tumor Dominance:

- DOM+ (OSE origin): Tumor was limited to one ovary or the size of one involved ovary exceeded the other by more than two times.
- DOM- (tubal origin): Disease was equally distributed across the peritoneal cavity.

METHODS

Statistical Analysis:

- Cox proportional hazards regression, stratified by site of origin and time period (NHS) and multinomial logistic regression (NECC), was used to examine the associations between reproductive/hormonal and non-reproductive exposures with risk of DOM+ versus DOM- tumors.
- Multivariate models were adjusted for age, matching factors, OC use, parity, tubal ligation, and family history of breast or ovarian cancer
- Endometriosis was not available in NHS, therefore, endometriosis effect estimates are restricted to NECC.
- For each exposure, we calculated the *p*-value for heterogeneity using a likelihood ratio test comparing models with separate estimates for the two subtypes versus a single estimate across subtypes[2].
- NECC and NHS estimates were combined using meta-analysis; Q tests showed no differences between studies.

RESULTS

- Among the 1704 invasive epithelial ovarian cancer cases, we observed 1048 tumors (778 NEC, 270 NHS) with a dominant mass, indicating a greater likelihood of ovarian origin, and 656 (534 NEC, 122 NHS) with no dominant mass, indicating a greater likelihood of fallopian tube origin. The dominant cases were more likely to be mucinous, endometrioid, clear cell, or undifferentiated while the non-dominant cases were more likely to be serous ovarian cancers, except for serous borderline tumors which were more likely to be dominant.

Table 1. Association between reproductive exposures and risk of epithelial ovarian cancer by cell of origin, NHS (1976-2006), NHSII (1989-2007), and NECC (1992-2008)

Variable	DOM+ RR (95%CI)	DOM- RR (95%CI)
OC use		
Never	Ref	Ref
< 5 years	0.86 (0.65, 1.13)	0.93 (0.76, 1.13)
≥ 5 years	0.65 (0.35, 1.22)	0.55 (0.37, 0.73)
IUD use	0.83 (0.65, 1.05)	1.71 (0.64, 4.57)
Tubal ligation	0.60 (0.49, 0.75)	1.02 (0.81, 1.28)
Hysterectomy	0.67 (0.53, 0.86)	0.87 (0.65, 1.15)
Parity		
None	Ref	Ref
One	0.60 (0.47, 0.76)	0.62 (0.45,0.85)
Two	0.48 (0.36, 0.65)	0.67 (0.52, 0.85)
Three	0.32 (0.26, 0.41)	0.57 (0.43, 0.75)
≥ Four	0.28 (0.19, 0.39)	0.49 (0.26, 0.92)
Endometriosis	1.49 (1.12, 1.97)	0.68 (0.45, 1.02)

RESULTS

Table 2. Association between non-reproductive exposures and risk of epithelial ovarian cancer by cell of origin , NHS (1976-2006), NHSII (1989-2007), and NECC (1992-2008)

Variable	DOM+ RR (95%CI)	DOM- RR (95%CI)
Body mass index (kg/m^2)		
<23	Ref	Ref
23-24	0.98 (0.80, 1.19)	1.07 (0.59, 1.93)
25-29	0.94 (0.76, 1.16)	0.78 (0.58, 1.04)
≥30	1.15 (0.94, 1.40)	1.04 (0.76, 1.41)
Smoking		
Never	Ref	Ref
Past	0.97 (0.83, 1.13)	1.25 (1.04, 1.51)
Current	1.30 (1.02, 1.66)	1.37 (1.06, 1.77)
Aspirin use	0.99 (0.83, 1.18)	0.73 (0.46, 1.15)
Acetaminophen use	1.24 (1.05, 1.47)	0.90 (0.60, 1.34)
Other NSAID use	0.88 (0.74, 1.04)	0.66 (0.53, 0.82)
Family hx of breast cancer	1.23 (1.01, 1.49)	1.19 (0.93, 1.51)
Family hx of ovarian cancer	1.40 (0.91, 2.16)	2.32 (1.54, 3.49)

- In the NECC study, we observed significantly different risk between tumor types for IUD use (p=0.05), tubal ligation (p=0.001), parity (p=0.001), and endometriosis (p=0.0002), but not other exposures.
- Results were similar when restricted to serous tumors.

CONCLUSIONS

- Our results suggest that tubal ligation and parity may be more strongly associated with tumors of ovarian origin, while family history of ovarian cancer and possibly past smoking primarily increases risk of tumors of tubal origin. Our data suggest aspirin and NSAID use may be more strongly associated with tubal tumors.
- Characterizing risk factor relationships by tumor dominance may elucidate how these exposures alter risk and help to improve prevention efforts.

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2. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epi 2010;171(1):45-53.*

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Appendix B

Epidemiologic predictors of tumor dominance in ovarian cancer, a surrogate for cell of origin

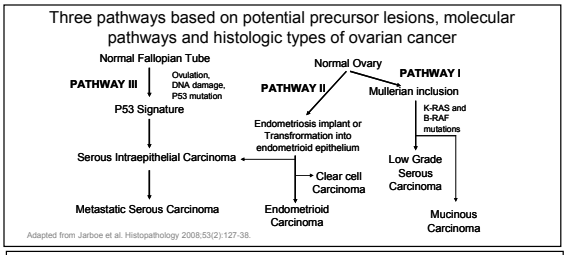
Katie Terry

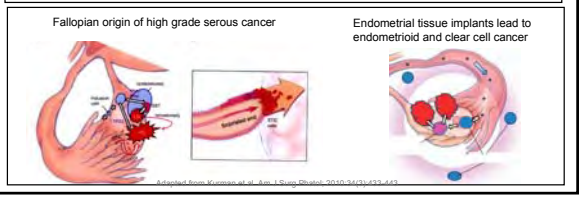
Gyn/Onc Seminar

April 13, 2011

Background

- Ovarian cancers originally thought to arise from ovarian surface epithelium
- Recent evidence suggests some ovarian cancers may arise from fallopian tubes
- Combining ovarian cancers that arise through independent pathways may obscure true associations





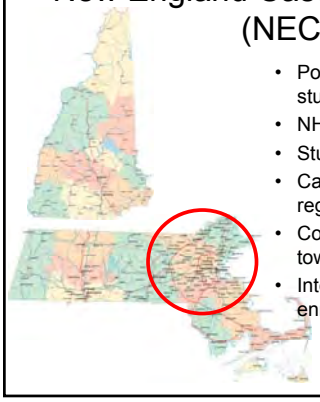
Dominance and cell of origin

- Detailed sectioning is required to identify cell of origin (SEE-FIM protocol) which is not practical in population based studies
- Presence of a dominant ovarian mass (DOM+) is significantly associated with serous tubal intraepithelial carcinoma (STIC), p = 0.001
- Therefore, dominance of tumor, ascertained from pathology reports, could serve as a proxy for cell of origin

Roh et al. Am J Surg Pathol 2009;3(3):376-83

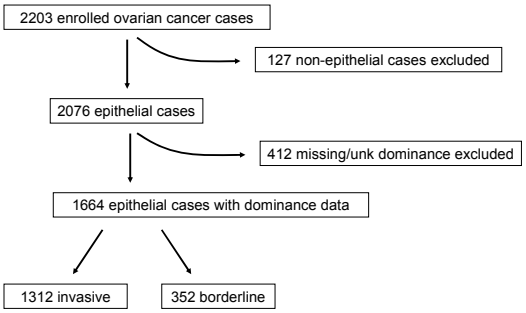
Study populations

New England Case-Control Study (NECC)



- Population based case-control study
- NH and eastern MA
- Study period: 1992 – 2008
- Cases –tumor boards & cancer registries
- Controls – random-digit dialing, town books, driver's license lists
- Interview and blood collection at enrollment

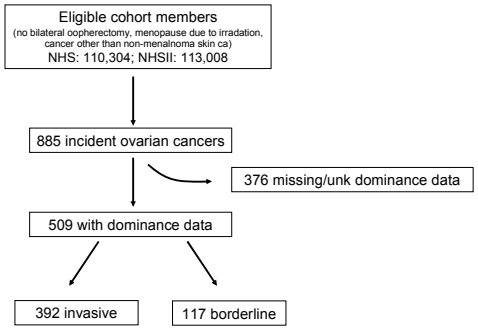
New England Case Control ovarian cancer cases



Nurses' Health Studies

- Nurses' Health Study (NHS): 121,700 female registered nurses aged 30-55 followed since 1976
- NHSII: 116,430 female registered nurses aged 25-42 followed since 1989
- Risk factor data and disease outcomes collected by biennial mailed questionnaires
- Incident cases of epithelial ovarian cancer identified by questionnaire or death records from 1976-2006 (NHS) and 1989-2007 (NHSII)

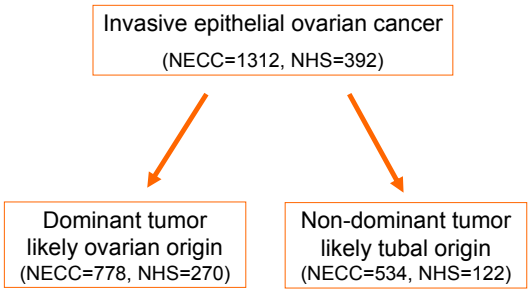
Nurses Health Studies



Classification of tumor dominance

- Dominant (i.e. OSE origin): tumor limited to one ovary or one involved ovary exceeded the other in dimension by more than 2x
- Non-dominant (i.e. tubal origin): disease was equally distributed across the peritoneal cavity

Outcome



Exposures to be considered

- Reproductive
  - Oral contraceptive use
  - IUD use
  - Tubal ligation
  - Parity
  - Breastfeeding
  - Mastitis
  - Infertility
  - Endometriosis
- Non-reproductive
  - Body mass index
  - Smoking
  - Talc use
  - NSAIDs
  - Family history
    - Breast cancer
    - Ovarian cancer

Statistical analysis

- NECC: polytomous (multinomial) logistic regression
  - STATA mlogit command
- NHS: Cox proportional hazards regression
  - SAS proc phreg command
- Both analyses stratified by dominance (+/-)
- Adjusted for ovarian cancer risk factors
  - age
  - oral contraceptives
  - Parity
  - tubal ligation
  - family history breast or ovarian cancer
- For each exposure, we compared model with separate estimates for the two subtypes to model with single estimate across subtypes using likelihood ratio test to determine p for heterogeneity

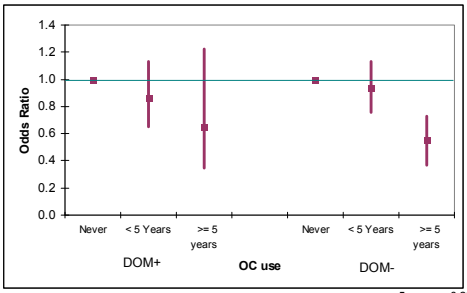
RESULTS

Histologic distribution by dominance, New England Case-control study (1992-2008)

Histology	Dominant n=1062 n (row %)	Non-dominant n=602 n (row %)
Serous		
Borderline	142 (71)	59 (29)
Low grade	52 (42)	73 (58)
High grade	193 (37)	326 (63)
Unknown, missing, ungraded	10 (45)	12 (55)
Mucinous		
Borderline	112 (97)	3 (3)
Invasive	79 (96)	3 (4)
Endometrioid	226 (82)	48 (18)
Clear Cell	178 (81)	42 (19)
Other/undifferentiated	70 (66)	36 (34)

Reproductive exposures

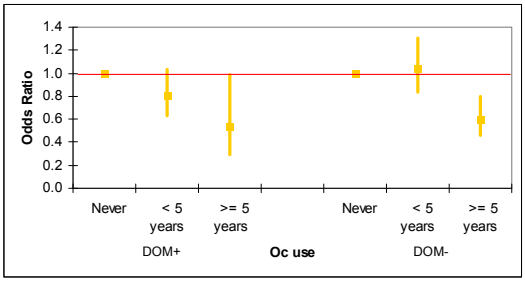
Association between oral contraceptive use and risk of epithelial ovarian cancer by tumor dominance



< 5 yrs p_{het}=0.22

≥ 5 yrs p_{het}=0.71

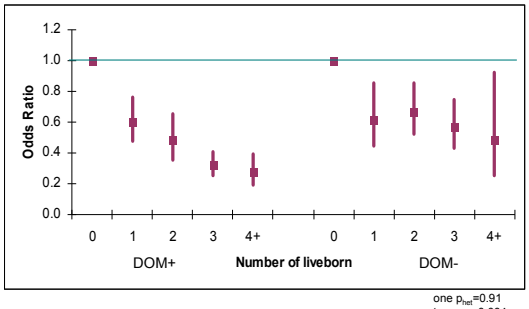
Association between oral contraceptive use and risk of serous tumors by tumor dominance



< 5 yrs p_{het}=0.07

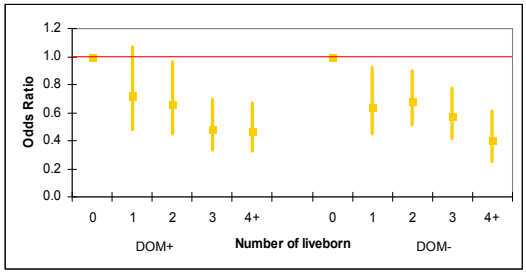
≥ 5 yrs p_{het}=0.20

Association between parity and risk of epithelial ovarian cancer by tumor dominance



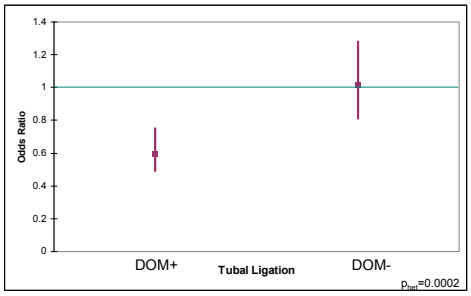
one p_{het}=0.91
two p_{het}=0.004
three p_{het}=0.0003
≥ four p_{het}=0.004

Association between parity and risk of serous tumors by tumor dominance

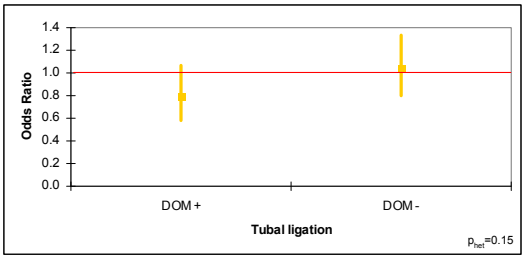


one p_{het}=0.60
two p_{het}=0.66
three p_{het}=0.40
≥ four p_{het}=0.42

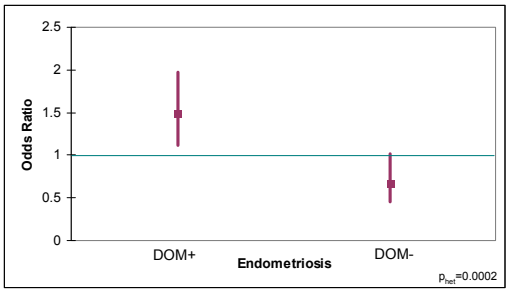
Association between tubal ligation and risk of epithelial ovarian cancer by tumor dominance



Association between tubal ligation and risk of serous tumors by tumor dominance

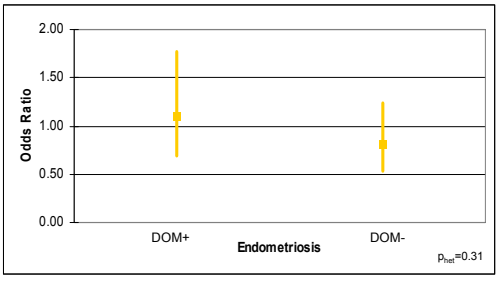


Association between endometriosis and risk of epithelial ovarian cancer by tumor dominance*



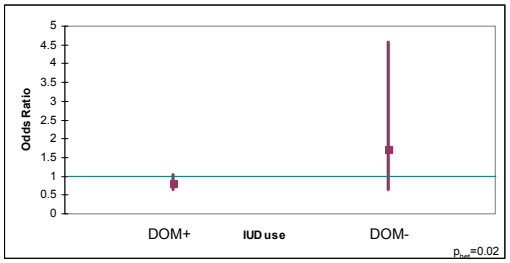
*based on NECC only

Association between endometriosis and risk of serous tumors by tumor dominance

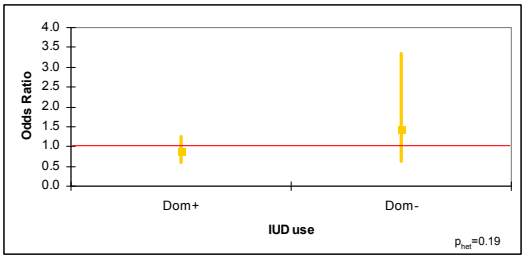


*based on NECC only

Association between IUD use and risk of epithelial ovarian cancer by tumor dominance



Association between IUD use and risk of serous tumors by tumor dominance



Duration of IUD use and ovarian cancer risk, NHS

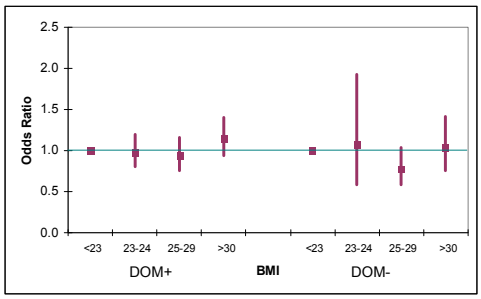
IUD duration	DOM+	DOM-
Never	1.00	1.00
Short	1.12 (0.59-2.13)	0.77 (0.24-2.42)
Long	0.92 (0.30-2.90)	4.18 (1.83-9.57)

Duration of IUD use and ovarian cancer risk, NECC

IUD duration	DOM+	DOM-
Never	1.00	1.00
<1 year	0.99 (0.66-1.48)	1.12 (0.72-1.76)
1-3 yrs	0.60 (0.36-1.00)	1.17 (0.72-1.85)
4-6 yrs	0.57 (0.30-1.08)	1.09 (0.61-1.95)
>6 yrs	1.00 (0.66-1.52)	1.11 (0.69-1.78)

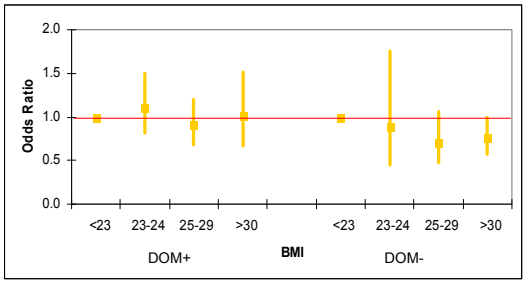
Non-reproductive exposures

Association between body mass index (kg/m$^{2)}$ and risk of serous ovarian cancer by tumor dominance



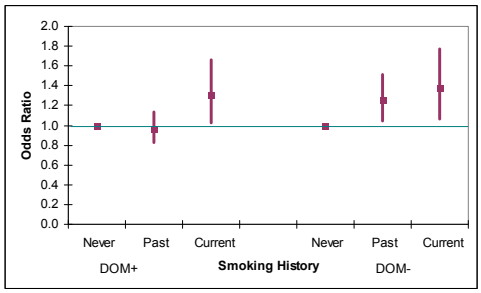
23-24 p_{het} = 0.72
25-29 p_{het} = 0.05
≥ 30 p_{het} = 0.26

Association between body mass index (kg/m^2) and risk of epithelial ovarian cancer by tumor dominance



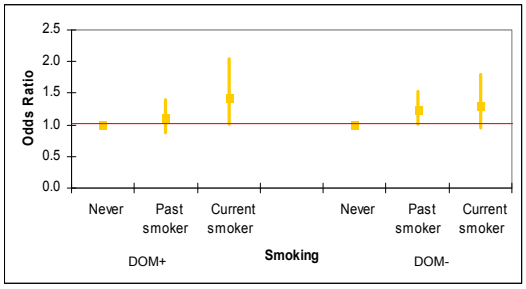
23-24 p_{het} = 0.09
25-29 p_{het} = 0.09
≥ 30 p_{het} = 0.08

Association between smoking and risk of epithelial ovarian cancer by tumor dominance



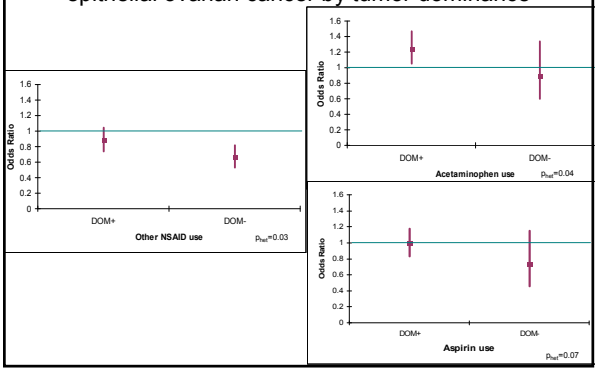
past p_{het} = 0.02
current p_{het} = 0.95

Association between smoking and risk of serous ovarian cancer by tumor dominance

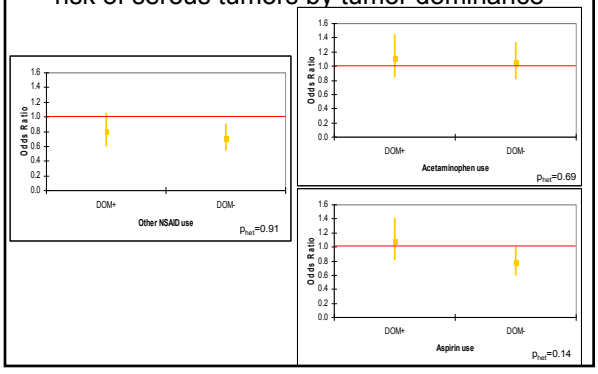


past p_{het} = 0.48
current p_{het} = 0.44

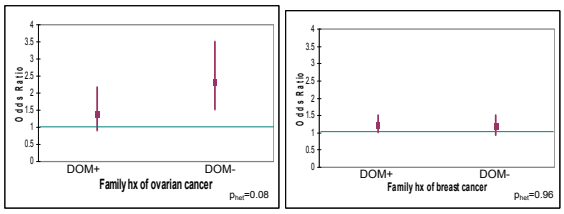
Association between pain reliever use and risk of epithelial ovarian cancer by tumor dominance



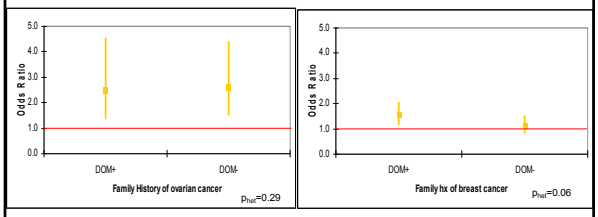
Association between pain reliever use and risk of serous tumors by tumor dominance



Association between family history of ovarian or breast cancer and risk of epithelial ovarian cancer by tumor dominance



Association between family history of breast or ovarian cancer and risk of serous tumors by tumor dominance



Conclusions

- DOM+ tumors (ovary)
  - more strongly associated with
    - tubal ligation
    - endometriosis
    - multiparity
  - IUD use associated with decreased risk
- DOM- tumors (tubal)
  - more strongly associated with:
    - NSAID use
    - family history of ovarian cancer
  - IUD use associated with increased risk
  - IUD/NSAID associations suggest inflammatory pathway for non-dominant tumors should be considered

Next steps

- Evaluate whether inflammatory markers differ by tumor dominance (measured in NHS blood cohort)
- Evaluate whether genetic susceptibility to ovarian cancer differs by tumor dominance (ex. Telomere maintenance SNPs)

Acknowledgements

- Ob/Gyn Epidemiology
  - Dan Cramer
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  - Kwaku Kyere

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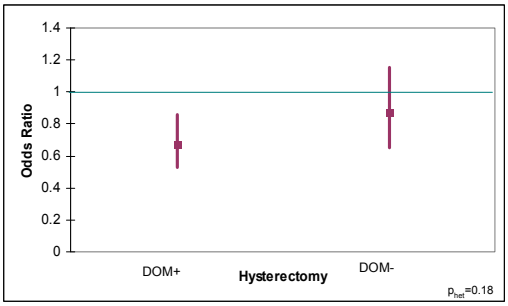
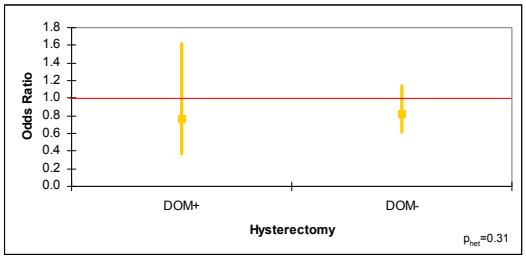
Stage by tumor dominance, NECC

Stage	Dominant n=778 n (col %)	Non-dominant n=534 n (col %)	Missing n=328 n (col %)
1	398 (51)	43 (8)	79 (24)
2	114 (15)	39 (7)	32 (10)
3	250 (32)	414 (78)	204 (62)
4	14 (2)	38 (7)	9 (3)
Missing	2 (<1)	0 (0)	4 (1)

Association between hysterectomy and risk of epithelial ovarian cancer by tumor dominance

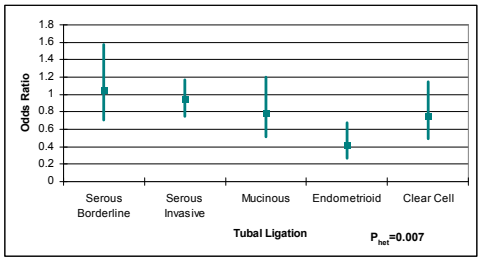


Association between hysterectomy and risk of serous tumors by tumor dominance

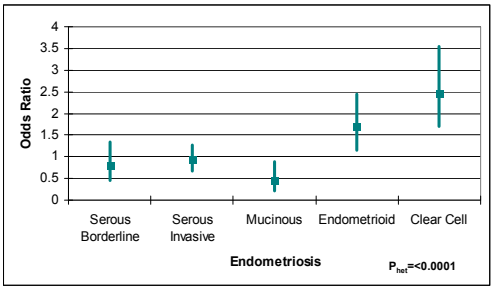


By histologic type

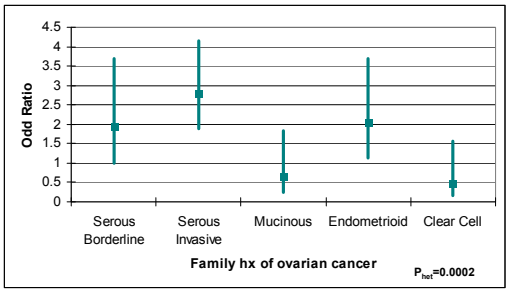
Association between tubal ligation and risk of epithelial ovarian cancer



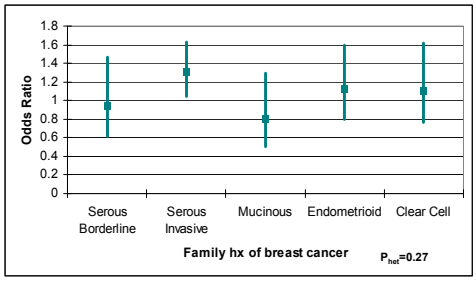
Association between endometriosis and risk of epithelial ovarian cancer



Association between family history of ovarian cancer and risk of epithelial ovarian cancer



Association between family history of breast cancer and risk of epithelial ovarian cancer



Associations between ovulatory cycles and histologic subtypes of ovarian cancer, New England Case-Control study (1992-2008)

Variable	Serous Borderline OR (95% CI)* n=246	Serous Invasive OR (95% CI)* n=868	Mucinous OR (95% CI)* n=239	Endometrioid OR (95% CI)* n=324	Clear Cell OR (95% CI)* n=359
Ovulatory cycles					
≤ 292	1.00	1.00	1.00	1.00	1.00
293-382	1.25 (0.84, 1.85)	1.55 (1.18, 2.04)	0.77 (0.50, 1.18)	2.40 (1.62, 3.57)	1.99 (1.28, 3.08)
382-444	1.22 (0.76, 1.95)	2.00 (1.51, 2.64)	1.13 (0.72, 1.78)	3.11 (2.03, 4.77)	2.78 (1.75, 4.43)
> 444	1.49 (0.90, 2.47)	2.38 (1.79, 3.16)	1.27 (0.78, 2.06)	4.06 (2.61, 6.31)	4.01 (2.49, 6.46)

Meta analysis summary

Variables	Dominant Invasive Tumors OR	Lower CI	Upper CI	Non-Dominant Invasive Tumors OR	Lower CI	Upper CI	Dom Serous Tumors Estimate	Lower CI	Upper CI	Non-dom serous tumors Estimate	Lower CI	Upper CI
Reproductive												
OC use												
Never												
< 5years	0.86	0.65	1.13	0.93	0.76	1.13	0.81	0.63	1.04	1.04	0.83	1.30
≥ 5 years	0.65	0.35	1.22	1.27	0.45	3.56	0.54	0.30	0.99	0.60	0.46	0.79
UD use	0.83	0.65	1.05	1.71	0.64	4.57	0.86	0.60	1.25	1.44	0.62	3.35
Tubal ligation	0.60	0.49	0.75	1.02	0.81	1.28	0.79	0.58	1.07	1.03	0.80	1.33
Hysterectomy	0.67	0.53	0.86	0.87	0.65	1.15	0.77	0.36	1.62	0.84	0.61	1.14
Parity												
Nulliparous												
One	0.60	0.47	0.76	0.62	0.45	0.85	0.72	0.48	1.07	0.64	0.45	0.92
Two	0.48	0.36	0.65	0.67	0.52	0.85	0.66	0.45	0.96	0.68	0.51	0.90
Three	0.32	0.26	0.41	0.57	0.43	0.75	0.48	0.34	0.70	0.57	0.42	0.77
≥ Four	0.28	0.19	0.39	0.49	0.26	0.92	0.47	0.33	0.67	0.49	0.26	0.62
Non-reproductive												
BMI												
<23												
23-24	0.98	0.80	1.19	1.07	0.59	1.93	1.11	0.82	1.49	0.88	0.45	1.75
25-29	0.94	0.76	1.16	0.78	0.58	1.04	0.91	0.69	1.19	0.71	0.47	1.06
≥30	1.15	0.94	1.40	1.04	0.76	1.41	1.01	0.67	1.51	0.76	0.57	1.00
Smoking												
Never												
Past smoker	0.97	0.83	1.13	1.25	1.04	1.51	1.10	0.87	1.40	1.24	1.01	1.53
Current smoker	1.30	1.02	1.66	1.37	1.06	1.77	1.44	1.01	2.05	1.30	0.95	1.79
Aspirin use‡	0.99	0.83	1.18	0.73	0.46	1.15	1.08	0.83	1.40	0.78	0.61	1.00
Acetaminophen	1.24	1.05	1.47	0.90	0.60	1.34	1.11	0.86	1.43	1.05	0.83	1.33
Other NSAID use‡	0.88	0.74	1.04	0.66	0.53	0.82	0.80	0.61	1.05	0.71	0.55	0.90
Family hx breast ca	1.23	1.01	1.49	1.19	0.93	1.51	1.57	1.19	2.06	1.13	0.87	1.48
Fam hx of ovarian ca	1.40	0.91	2.16	2.32	1.54	3.49	2.51	1.39	4.53	2.61	1.54	4.39